Dear Healthcare Professionals,

Bendamustine: increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections and hepatitis B reactivation

Your attention is drawn to the UK Medicines and Healthcare products Regulatory Agency’s (MHRA) announcement that bendamustine was associated with increased mortality and an unfavourable safety profile when used in combination with rituximab or obinutuzumab in clinical trials of non-approved combination therapies. Deaths were mainly due to infections including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia, varicella zoster virus, and cytomegalovirus infection. Some fatal cardiac, neurological, and respiratory toxicities were also reported.

Regarding post-marketing data, a recent European review has suggested that the risk of opportunistic infections with bendamustine treatment may be greater than previously recognised. Infections include bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia, varicella zoster virus, and cytomegalovirus infection. Both the frequency and outcome of infections seem to be highly variable and dependent on the clinical setting. Reactivation of hepatitis B virus in chronic carriers of the virus has been reported after bendamustine. Some cases resulted in acute hepatic failure or a fatal outcome.

Healthcare professionals are advised:

- to advise patients to report promptly new signs of infection, including fever or respiratory symptoms, and consider discontinuing bendamustine if there are signs of opportunistic infections;
- to monitor patients for opportunistic infections as well as cardiac, neurological, and respiratory adverse events;
- hepatitis B virus (HBV) reactivation has also been reported; monitor known carriers of HBV for signs and symptoms of active HBV infection;
- increased mortality (mainly due to opportunistic infections) was observed in recent clinical studies when bendamustine was used in combination treatment outside the approved indications; and
- to report suspected adverse reactions associated with bendamustine to MHRA on a Yellow Card.
Please refer to the following website in MHRA for details:

In Hong Kong, there are 2 registered pharmaceutical products containing bendamustine, namely Treanda For Inj 100mg (HK-59067) and Treanda For Injection 25mg (HK-62300). These products are registered by Ivax Asia Ltd, and are prescription-only medicines. So far, the Department of Health (DH) has received one case of adverse drug reaction related to bendamustine, but it was not related to infection. DH will remain vigilant on safety update of bendamustine issued by other overseas drug regulatory authorities. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under “ADR Reporting”: http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)
for Assistant Director (Drug)